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Letters

Pesticides, Risk, and Applesauce

The tremendous attention in the media to the growth-regulator Alar raises important issues about the nation's efforts to prevent human cancer by regulating chemicals that are carcinogenic in animal studies. Leslie Roberts, in her Research News articles "Pesticides and kids" (10 Mar., p. 1280) and "Is risk assessment conservative?" (24 Mar., p. 1553), did not address several points that we think are important for putting possible risks in perspective.

1) *Pesticides, 99.99% all natural.* Although regulatory efforts are focused on identifying and controlling synthetic chemicals that are estimated to pose a possible carcinogenic risk to society greater than one in a million (such as Alar), we are ingesting about 10,000 times more natural than synthetic pesticides (*1*). All plants produce toxins to protect themselves against fungi, insects, and predators such as man (*2, 3*). Tens of thousands of these natural pesticides have been discovered, and every species of plant contains its own set of different toxins, usually a few dozen. When plants are stressed or damaged, such as during a pest attack, they increase their natural pesticide levels manyfold, occasionally to levels that are acutely toxic to humans (*4*). Very few of these plant toxins have been tested in animal cancer bioassays, but among those tested, about half (20/42) are carcinogenic (*4, 5*).

It is probable that almost every plant product in the supermarket contains natural carcinogens. The following foods contain natural pesticides that cause cancer in rats or mice and are present at levels ranging from a few parts per billion to 4 million parts per billion (ppb) (*3, 4*): anise, apples, bananas, basil, broccoli, Brussels sprouts, cabbage, cantaloupe, carrots, cauliflower, celery, cinnamon, cloves, cocoa, comfrey tea, fennel, grapefruit juice, honeydew melon, horseradish, kale, mushrooms, mustard, nutmeg, orange juice, parsley, parsnips, peaches, black pepper, pineapples, radishes, raspberries, tarragon, and turnips. Of the pesticides we eat, 99.99% are all natural, and, like man-made pesticides, most are relatively new to the modern diet because of the exchange of plant foods among the Americas, Europe, Asia, and Africa within the last 1000 years. It is reassuring, however, that the many layers of general defenses in humans and other animals (*1, 6, 7*) protect against toxins, without distinguishing whether they are synthetic or natural.

2) *Trade-offs.* In response to fears about residues of man-made pesticides, plant breeders are active in developing varieties that are naturally pest-resistant. Such varieties contain increased amounts of natural pesticides. It should be no surprise, then, that a newly introduced variety of insect-resistant potato had to be withdrawn from the market, due to acute toxicity to humans caused by much higher levels of the teratogens solanine and chaconine than are normally present in potatoes (*8*). Similarly, a new variety of insect-resistant celery recently introduced widely in the United States is causing outbreaks of dermatitis in produce workers due to a concentration of the carcinogen 8-methoxypsoralen (and related psoralens) of 9000 ppb, rather than the usual 900 ppb (*9*). Many more such cases are likely to crop up. Thus, there is a fundamental trade-off between nature's pesticides and man-made pesticides. The Environmental Protection Agency (EPA) has strict regulatory requirements for new synthetic pesticides and is steadily weeding out old substances such as Alar that are thought to pose a significant hazard; however, natural pesticides are almost completely neglected. Natural pesticides that are possibly hazardous to humans could easily be decreased by plant breeding.

Given the background of human exposures to natural carcinogens (*1–7*), the finding that about half the chemicals tested in rodents (whether synthetic or natural) are carcinogenic (*1, 5*), and the difficulties in risk assessment (discussed below), we have ranked possible hazards on a HERP index (daily *H*uman *E*xposure dose/*R*odent *P*otency dose, as a percent) in order to achieve some perspective on human exposure to the plethora of carcinogens (*1*). Our ranking suggests that carcinogenic hazards from current levels of pesticide residues or water pollution are likely to be minimal relative to the background levels of natural substances.

To put Alar in perspective, we estimate that the possible hazard from UDMH (the carcinogenic breakdown product of Alar) in a daily lifetime glass (6 ounces) of apple juice is HERP = 0.0017% (*10*). This possible hazard is less than that from the natural carcinogenic hydrazines consumed in one daily mushroom (HERP = 0.1%) (*1*) or that from aflatoxin in a daily peanut butter sandwich (HERP = 0.03%) (*1*). It is also less than other possible hazards from natural carcinogens in food, although few have been tested. These include 8-methoxypsoralen in a daily portion (100 grams) of celery (*3, 11*), allyl isothiocyanate in a daily portion of cabbage or Brussels sprouts (*3, 12*), and alcohol in a daily glass of orange juice (*13*). The possible hazard of UDMH in a daily apple is 1/10 that of a daily glass of apple juice. Other HERP comparisons are shown in (*1*). Apple juice has been reported to contain 137 natural volatile chemicals (*14*), of which only five have been tested for carcinogenicity (*5*); three of these—benzyl acetate, alcohol, and acetaldehyde—have been found to be carcinogenic.

The EPA has proposed cancellation hearings on Alar, and the Natural Resources Defense Council (NRDC) is trying to speed this process up by a year or two. The trade-offs must be considered in efforts to prevent hypothetical carcinogenic risks of 10^{-6} or 10^{-5}, because the results could be counterproductive if the risks of the alternatives are worse. What risks might we incur by banning Alar? Alar is a growth regulator that delays ripening of apples so that they do not drop prematurely, and it also delays overripening in storage. Alar plays a role in reducing pesticide use for some types of apples, particularly in the Northeast (*15*).

For example, without Alar, the danger of fruit fall from leafminers is greater, and more pesticides are required to control them. Also, when apples fall prematurely, pests on the apples remain in the orchard to attack the crop the next summer, and more pesticides must be used. Since Alar produces firmer apples, and results in fewer falling to the ground, treated fruit may be less susceptible to molds. Therefore, it is possible that the amounts and variety of mold toxins present in apple juice, for example, patulin (*16*), will be higher in juice made from untreated apples. The carcinogenicity of patulin has not been adequately examined (*17*). The EPA should, as NRDC emphasizes, also take into consideration that children consume large amounts of apple juice. Another trade-off is that fewer domestically grown, fresh apples would be available throughout the year, and the price would be higher; thus, consumers might substitute less healthy foods.

3) *Risk assessment.* Currently, neither theory nor experimental evidence is adequate to guide scientists in extrapolating from rodent cancer tests at the maximum tolerated dose (MTD) to human exposures that are thousands or millions of times lower. Therefore, for prudence's sake, federal regulatory agencies routinely make worst-case assumptions to estimate the upper limit on risk for low doses; however, the real risks at low doses may well be zero. Conventional risk assessments at the low levels of human exposure thus are really quite speculative (*1*) and should not be viewed as if they were real risks. Accumulating scientific evidence (*1, 6, 7, 18*) suggests that chemicals administered in animal cancer tests at the MTD are causing cancer in quiescent tissues primarily by increasing cell proliferation, an essential aspect of carcinogenesis for both mutagens and nonmutagens. Because endogenous rates of DNA damage are enormous (*6*), cell proliferation alone is likely to be tumorigenic. Cell proliferation converts DNA adducts (either spontaneous or exogenous) to mutations or to epimutations (such as loss of 5-methylC) and exposes single-stranded DNA, a much more sensitive target for mutagens. It also allows mutant cells to escape from growth inhibition signals coming from surrounding cells (*1, 6, 7*).

If animal cancer tests are primarily measuring cell proliferation, then the dose-response curve should fall off sharply with dose, even for mutagens [as with diethylnitrosamine (*18*)] and should have a threshold for nonmutagens. Thus, the hazards at low doses could be minimal. Furthermore, humans have numerous inducible defense systems against mutagenic carcinogens, such as DNA repair, antioxidant defenses, glutathione transferases, and so forth, which may make low doses of mutagens protective in some circumstances. Even radiation—the classical DNA-damaging agent and carcinogen—may be protective in small doses against DNA damage at higher doses, as shown by recent work in human cells (*19*). Also, recent radiation experiments in mice show a dose threshold for the latency of tumor appearance (*20*). Thus, low doses of carcinogens appear to be both much more common and less hazardous than is generally thought. These scientific questions about mechanisms of carcinogenesis and the preventable causes of human cancer, in any case, are being resolved by the scientific community as quickly as resources allow.

Regulation of low-dose exposures to chemicals based on animal cancer tests may not result in significant reduction of human cancer, because we are exposed to millions of different chemicals—almost all natural—and it is not feasible to test all of them. Most exposures, with the exception of some occupational, medical, or natural pesticide exposures, are at low doses. The selection of chemicals to test, a critical issue, should reflect human exposures that are at high doses relative to their toxic doses and the numbers of people exposed. Epidemiology has been reasonably successful in identifying risk factors for human cancer, such as smoking, hormonal and dietary imbalances, asbestos, and several occupational chemicals; the data suggest that pesticide residues are unlikely to be a significant risk factor (*6, 21*). Epidemiology, with molecular approaches, is becoming more sophisticated and will continue to be our main tool in analyzing causes of cancer. In order to minimize cancer and the other degenerative diseases of aging [which are associated with our constantly increasing life expectancy (*6, 7*)], we need to obtain the knowledge that will come from further basic scientific research.

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